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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,694	02/10/2004	Irit Gil-Ad	25464X	8587

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EXAMINER

OLSON, ERIC

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/774,694	Applicant(s) GIL-AD ET AL.	
	Examiner Eric S. Olson	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 26 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-69 is/are pending in the application.
- 4a) Of the above claim(s) 16-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 and 61-69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>July 19, 2004</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

This application is a continuation-in-part of US application 10/432875, filed September 16, 2003, currently pending, which is a national stage application of PCT/IL01/01105, filed November 29, 2001, which claims benefit of foreign application IL 139975, filed November 29, 2005.

Election/Restrictions

Applicant's election without traverse of group I, drawn to a pharmaceutical composition comprising a topically acceptable carrier and a cyclic psychotropic agent other than doxepine or tomoxetine, filed September 26, 2006, is acknowledged. Because the election was made without traverse, this requirement is therefore made FINAL.

Claims 1-69 are pending in this application and examined on the merits herein.

Applicant's amendment submitted September 26, 2006 is acknowledged wherein new claims 61-69 are introduced. Because these new claims are drawn to a pharmaceutical composition and depend from claim 1, they are examined together with group I.

Claims 16-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 26, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite the terms, "phenylpropylamine derivative," and "phenoxy-3-propylamine derivative." It is not clear from the claims or the specification what is the full extent of compounds included within these limitations. In particular, a derivative could mean, in the present context, any one of a number of chemical modifications including but not limited to:

- (1) Substitution of individual atoms or functional groups with equivalent atoms or functional groups.
- (2) Protection of one or more functional groups with a protecting group.
- (3) Attachment of one or more additional functional groups to the parent core structure.

Because the term "derivative" is not clearly and distinctly defined, this phrase renders the claims indefinite.

Claim 10 recites the limitation "wherein the phenothiazine is selected from the group consisting of thioridazine, perphenazine, trifluoperazine, and fluphenazine".

There is insufficient antecedent basis for this limitation in the claim. Claim 9, from which

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claim 10 depends, specifically defines the tricyclic antipsychotic drug as being phenothiazine, not a phenothiazine derivative as recited in claim 10. Thus claim 10 lacks antecedent basis in claim 9.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7, 8, 14, 15, and 61-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising certain specific antidepressant and antipsychotic agents such as those examples explicitly recited on pp. 15-16 of the instant specification, does not reasonably provide enablement for a composition comprising any cyclic psychotropic agent, any antidepressant or antipsychotic, or any serotonin and/or noradrenaline reuptake inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

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(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a composition of matter comprising an antidepressant or antipsychotic and a topically acceptable carrier.

The state of the prior art: There are a significant number of antidepressant and antipsychotic agents known in the art. These agents have been previously combined with appropriate carriers to produce creams, ointments, and other topical pharmaceutical compositions. However, the prior art does not provide an exhaustive listing of each and every possible chemical compound having antidepressant or antipsychotic activity, or a method of synthesizing each and every such compound. The prior art also does not indicate whether each and every possible cyclic psychotropic agent is useful as a topically acceptable composition.

The relative skill of those in the art: The relative skill in the art is high.

The predictability or unpredictability of the art: Although certain molecular targets, such as dopamine and serotonin, are known to be useful molecular targets for psychotropic agents, the brain is not fully understood to the point where the psychotropic activity or lack thereof for a particular compound may be determined in the absence of experimental data for that compound. Furthermore, the antiproliferative, analgesic, and other topical effects of psychotropic agents are not well understood to the point of being able to predict for certain whether a particular psychotropic agent possess any topical activity.

Furthermore, the art of chemical synthesis is unpredictable in that there exists no general method for synthesizing any desired compound regardless of structure. Rather, specific structures must be considered individually in order to develop an appropriate synthetic scheme.

Thus the subject matter encompassed by the claimed invention is highly unpredictable.

The Breadth of the claims: The claimed invention includes any pharmaceutical composition, such as an ointment, lotion, gel, spray, or eyedrop, comprising a cyclic psychotropic agent which is suitable for delivering the agent locally in high concentration without delivering a significant amount to systemic circulation.

The amount of direction or guidance presented: The instant specification lists a number of known cyclic psychotropic agents which are useful for treating proliferative disorders, and which could be incorporated into a topical pharmaceutical composition. No guidance is given for the discovery of novel cyclic psychotropic agents or the synthesis of candidate compounds for use in such a drug discovery program.

The presence or absence of working examples: Topical administration of psychotropic-containing pharmaceutical compositions is demonstrated in several patients on pp. 24-32 of the instant specification. No examples are given of the discovery of new cyclic psychotropic agents.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery and synthesis of new psychotropic agents. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of cyclic psychotropic agents beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as a cyclic psychotropic agent, as there exists no definitive *in vitro* test for psychotropic activity. Tests for antagonism of specific biological targets, such as dopamine receptors, are not capable of identifying each and every possible psychotropic agent. According to the 2006 Chemical Abstracts catalog, The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have psychotropic activity and to be cyclic according to p. 14, lines 1-6 of the instant specification. For most compounds, it is unknown whether they are or are not useful as cyclic psychotropic agents. Gathering this data for every compound known to man would involve *in vivo* screening of an enormous diversity of chemical compounds for psychotropic activity in animal subjects using models such as the rat forced swim test.

Such testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods

In vivo animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations,

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care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of cyclic psychotropic agents, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible cyclic psychotropic agent, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of cyclic psychotropic agents claimed.

Genentech, 108 F.3d at 1366, states that, “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion.” And “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.”

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of working examples, Applicants fail to provide information sufficient to practice the claimed invention for every possible cyclic psychotropic agent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 14, 15, and 61-69 are rejected under 35 U.S.C. 102(e) as being anticipated by Sawynok et al. (US patent 6211171, reference cited in PTO-892) Sawynok et al. discloses a composition comprising a specific tricyclic, second generation, or third generation antidepressant preferably formulated for local use, as a saline solution, cream, gel, or spray, for example, (column 4, lines 30-35, column 10, lines 37-67) as disclosed in instant claims 1-3 and 14-15. The antidepressant is preferably one of the tricyclic antidepressants including clomipramine, imipramine, or in an especially preferred embodiment amitriptyline, (column 9, line 66 – column 10 line 4) or a second or third generation antidepressant including trazodone, bupropion, or venlafaxane, (column 10, lines 33-36) as disclosed in instant claims 4-6. Although Sawynok et al. suggests that these compositions could be used for the treatment of neuropathic pain, the compositions comprise the same ingredients as those of the claimed invention disclosed to possess activity against proliferative dermatological diseases. Thus the compositions of Sawynok et al. are inherently the same as the

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claimed invention of instant claims 61-69. Therefore Sawynok et al. anticipates the instant claims.

Claims 1-4, 7-15, and 61-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Beltner. (EP0168626, reference included with PTO-892) Beltner discloses a composition comprising a topical ointment, cream, or lotion containing a compound having the ability to interfere with calcium calmodulin complex. (p. 3, lines 8-12) Beltner also discloses that two compounds known to have this activity, and thus to be useful in the claimed pharmaceutical compositions, are the antipsychotic drugs fluphenazine, chlorprothixene, and clozapine, as well as the antidepressants imipramine and amitriptyline. (p. 3, lines 1-6) Although Beltner suggests that these compositions could be used for the treatment of trauma of the skin, the compositions comprise the same ingredients as those of the claimed invention disclosed to possess activity against proliferative dermatological diseases. Thus the compositions of Beltner are inherently the same as the claimed invention of instant claims 61-69. Therefore Beltner anticipates the instant claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

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F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 14-15, and 61-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 65-75 of copending Application No. 10/432875. (Reference cited in PTO-892, herein referred to as '875) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 65-75 of '875 anticipate the instant claims.

Claims 65, 66, and 75 of '875 are drawn to a pharmaceutical composition for the treatment of proliferative skin disorders that is suitable for application to the affected skin, comprising a pharmaceutically acceptable carrier and a psychotropic agent. Claims 67-74 are drawn to these compositions comprising specific cyclic psychotropic agents, anticipating the compositions of instant claims 1-10, 14-15, and 61-69.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

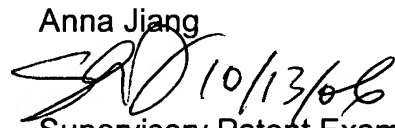
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson

Patent Examiner
AU 1623
10/4/06

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